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09/528,644	03/20/2000	Lars Thim	3951.224-US	5698

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/528,644	THIM ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-33,36 and 40-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-33,36 and 40-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *27-33,36 and 40-65* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 12/11/2003 has been entered. Claims 27-33, 36, 40-65 are pending.

Applicant's election of the species a homolog of SEQ ID NO: 1 wherein the homolog is identical to SEQ ID NO: 1 except for two amino acid substitutions, wherein the amino acid substitutions are in the first trefoil domain in the paper filed 12/11/2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 47, 49, 55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the paper filed 12/11/2003.

Maintained Formal Matters, Objections, and/or Rejections:

Claims 27-33, 36, 42-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a glycosylated polypeptide comprising the amino acid sequence of SEQ ID NO: 1, does not reasonably provide enablement for "homologue" useful for the treatment of ulcers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In addition the specification does not provide an assay for measuring usefulness in the treatment of ulcers. It is unclear what endpoint is intended by the limitation "useful in the treatment of ulcers."

It is further noted that a nucleic acid molecule that hybridizes to a nucleic acid molecule encoding SEQ ID NO: 1 is antisense to a nucleic acid molecule encoding SEQ ID NO: 1 and does not encode anything resembling SEQ ID NO: 1. The specification lacks guidance for, and working examples of, using such variant polypeptides for the treatment of ulcers.

Applicants argue that the present specification teaches how to make SEQ ID NO: 1 and refer to Playford et al. Applicant's arguments have been fully considered but they are not persuasive. A disclosure of SEQ ID NO: 1 in the present Applicant or in Playford is not commensurate with claimed "homologue." Furthermore, while a specification need not disclose what is well known in the art, that rule does not excuse an applicant from providing a complete disclosure. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Although certain claims are limited to the substitution of only two amino acids, the specification does not provide an assay for measuring usefulness in the treatment of ulcers and it is unclear what endpoint is intended by the limitation "useful in the treatment of ulcers."

Applicants argue that Bowie concludes that proteins are surprisingly tolerant of amino acid substitutions and that the test for undue experimentation is not merely quantitative. Applicant's arguments have been fully considered but they are not persuasive. Except for the deletion or creation of glycosylation sites, the instant specification does not identify those amino acid residues in the amino acid sequence of SEQ ID NO: 1 which are tolerant of amino acid

substitutions. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the amino acid sequence of SEQ ID NO: 1 which are required for the functional and structural integrity of that protein. It is this additional characterization of that single disclosed, naturally occurring protein that is required in order to obtain the functional and structural data needed to permit one to produce a "homologue" which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Applicant has taken the position that 35 U.S.C. § 112, first paragraph, permits an artisan to present claims of essentially limitless breadth so long as the specification provides one with the ability to test any particular embodiment which is encompassed by the material limitations of a claim and thereby distinguish between those embodiments which meet the functional limitations from those that don't. However, the issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance provide by the instant specification and the prior art of record. An inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements, while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of

enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. It is noted that there is not a single example in the instant specification, working or prophetic, of a "homologue" whose amino acid sequence deviates from nature other than the creation or deletion of a glycosylation site. The instant specification provides no working examples and no guidance that would permit an artisan to practice the invention commensurate with the scope of the instant claims. The first paragraph of 35 U.S.C. § 112 requires that the breadth of the claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them then the instant application does not support the breadth of the claims.

Claims 27-33, 36, 40-65 are rejected under 35 U.S.C. 112, second paragraph, over the recitation of "high stringency conditions." Applicants argue that the phrase would have a clear and definite meaning to one of skill in the art. Applicants arguments have been fully considered

but they are not persuasive. The present specification's reference to Sambrook is merely exemplary, and is not intended to limit the definition of "high stringency conditions" in any way.

Double Patenting

Claims 27-33, 36, 40, 41, 42-65 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10-13 of U.S. Patent No. 5,783,416 (a6). It is acknowledged that Applicants intend to submit a terminal disclaimer when the present application is allowable.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claims 27-30, 32, 40, 42, 43, 45, 46, 48, 50, 51, 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomasetto (2, cited by Applicants) in view of Podolsky (A), Alberts (u6), Hitzeman (x6), and Lodish (w6).

Tomasetto discloses the cDNA and deduced amino acid sequence of a human spasmolytic polypeptide (hSP) (paragraph bridging pages 409-410; Figure 5). The encoded protein contains a putative signal sequence, amino acids 1-24 (Figure 5). The amino acid sequence of the encoded protein minus the putative signal peptide is identical to Applicants' SEQ ID NO:1, as indicated below (Qy = Applicants' SEQ ID NO: 1) (Db = hSP):

```
RESULT    1
ENTRY             S12371     #type fragment
TITLE             spasmolytic protein 1 precursor - human (fragment)
ALTERNATE_NAMES   trefoil factor 2
ORGANISM          #formal_name Homo sapiens #common_name man
DATE              21-Nov-1993 #sequence_revision 24-May-1996 #text_change
                    18-Sep-1998
ACCESSIONS        S12371
REFERENCE         S12371
   #authors       Tomasetto, C.; Rio, M.C.; Gautier, C.; Wolf, C.; Hareuveni,
                    M.; Chambon, P.; Lathe, R.
   #journal       EMBO J. (1990) 9:407-414
   #title         hSP, the domain-duplicated homolog of pS2 protein, is
                    co-expressed with pS2 in stomach but not in breast
                    carcinoma.
   #cross-references MUID:90151615
```

```
   #accession     S12371
      ##molecule_type mRNA
      ##residues       1-130 ##label TOM
      ##cross-references EMBL:X51690; NID:g36558; PID:g36559
GENETICS
   #gene          GDB:TFF2; SML1
      ##cross-references GDB:128989; OMIM:182590
   #map_position 21q22.3
FUNCTION
   #description   inhibits gastrointestinal motility and gastric acid secretion
CLASSIFICATION    #superfamily spasmolytic protein; trefoil homology
KEYWORDS          duplication; hormone; pancreas
FEATURE
   1-24                #domain signal sequence (fragment) #status predicted
                         #label SIG\
   25-130              #product spasmolytic protein #status predicted #label
                         MAT\
   32-73               #domain trefoil homology #label TRF1\
   82-122              #domain trefoil homology #label TRF2\
   30-128,32-59,43-58,
   53-70,82-108,
   92-107,102-119      #disulfide_bonds #status predicted
SUMMARY           #length 130  #checksum 8997

  Query Match           100.0%;  Score 857;  DB 1;  Length 130;
  Best Local Similarity 100.0%;  Pred. No. 6.82e-177;
  Matches   106;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db      25 EKPSPCQCSRLSPHNRTNCGFPGITSDQCFDNGCCFDSSVTGVPWCFHPLPKQESDQCVM 84
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy       1 EKPSPCQCSRLSPHNRTNCGFPGITSDQCFDNGCCFDSSVTGVPWCFHPLPKQESDQCVM 60

Db      85 EVSDRRNCGYPGISPEECASRKCCFSNFIFEVPWCFFPNSVEDCHY 130
           ||||||||||||||||||||||||||||||||||||||||||||||
Qy      61 EVSDRRNCGYPGISPEECASRKCCFSNFIFEVPWCFFPNSVEDCHY 106.
```

hSP "has six disulfide bonds ... and 9-12" because hSP and SEQ ID NO: 1 are identical in structure or composition. Furthermore, a chemical composition and its properties are inseparable. hSP is encoded by a nucleic acid sequence that is at least 60% homologous to a nucleic acid sequence that encodes SEQ ID NO: 1 because the amino acid sequence of hSP and SEQ ID NO: 1 are identical. The nucleic acid sequence encoding hSP also encodes SEQ ID NO: 1. Therefore, the nucleic acid sequence encoding hSP would hybridize under high stringency conditions to complement of the nucleic acid sequence encoding SEQ ID NO: 1. hSP contains the amino acid sequence Asn-X-Ser/Thr, wherein X is any amino acid, at amino acid residues 39-41, which is a classic N-linked glycosylation site. Amino acid residues 39-41 of hSP correspond to amino acids 15-17 of Applicants' SEQ ID NO:1. Tomasetto discloses strong conservation of primary structure between PSP, mSP and hSP which suggest that these three proteins fulfill similar biological functions (page 412, column 2, full paragraph 4). Tomasetto does not teach an isolated hSP polypeptide which is in N-glycosylated form, in the sense that Tomasetto does not anticipate the claimed invention.

Podolsky teaches rat intestinal trefoil factor (rITF), which has significant homology to pS2 and porcine pancreatic spasmolytic peptide (PSP). PSP and pS2 are both thought to fold into a characteristic structure referred to as a trefoil. A trefoil structure consists of three loops formed by three disulfide bonds. pS2 is thought to include one trefoil, and PSP is thought to include two trefoils. The region of rITF which is most similar to PSP and pS2 includes six cysteines all of which are in the same position as the cysteines which make up the trefoil in pS2. Five of these six cysteines are in the same position as the cysteines which form the amino terminal trefoil of PSP. Paragraph bridging columns 4-5. The isolated hITF gene can be cloned into a mammalian expression vector for protein expression. This vector can be used to express the protein in COS cells, CHO cells, or mouse fibroblasts. The gene may also be cloned into a vector for expression in Drosophila cells using the baculovirus expression system. Column 8, lines 40-51. Podolsky also discloses a therapeutic composition that includes an intestinal trefoil factor and a pharmacologically acceptable carrier (column 1, lines 39, 41, 58-60; claim 3). Podolsky does not teach an isolated hSP polypeptide which is in N-glycosylated form, in the sense that Podolsky does not anticipate the claimed invention.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to clone a nucleic acid molecule encoding hSP, as taught by Tomasetto, and to modify that teaching by cloning the hSP nucleic acid molecule into a mammalian expression vector and express the nucleic acid molecule in mammalian cells, as taught by Podolsky, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because expression in mammalian cells is useful for the expression of trefoil proteins. Recombinant expression of hSP in mammalian cells would have

the advantage of providing a large amount of readily purified hSP. In so doing one of ordinary skill in the art would obtain an isolated hSP polypeptide which is in N-glycosylated form, glycosylated at an Asn present at position 15, comprising a glycosylated side chain comprising at least one hexose unit, wherein the glycosylated side chain comprises at least one mannose unit, wherein the glycosylated form comprises two units of GlcNAc, containing 39 amino acids in the first trefoil domain, containing 38 amino acids in the second trefoil domain. The invention is prima facie obvious over the prior art.

Alberts, Hitzeman, and Lodish are cited as evidence of what was in the public's possession before applicant's invention.

Alberts teaches that most of the soluble proteins that are secreted are glycoproteins (page 589, penultimate paragraph).

Hitzeman teaches N-linked glycosylation at the amino acid sequence Asn-X-Ser/Thr wherein X is any amino acid (page 436, full paragraph 2).

Lodish teaches that most secreted proteins are glycosylated (page 699, column 2, full paragraph 3), that in all N-linked oligosaccharides N-acetylglucosamine is linked to Asn (page 700, column 1, first full sentence), that N-linked oligosaccharides always contain mannose as well as N-acetylglucosamine (page 700, column 1, third sentence), that two GlcNAc and three Man are always found in *N*-linked oligosaccharides (page 701, legend to Figure 16-27), and that N-linked oligosaccharides can have as many as 60 mannose residues in yeast (page 701, legend to Figure 16-27).

Claims 27, 36, 40, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomasetto (2, cited by Applicants) in view of Podolsky (A), Alberts (u6), Hitzeman (x6), and Lodish (w6), as applied to claims 27 and 40 above, and further in view of Jorgensen.

Tomasetto in view of Podolsky, Alberts, Hitzeman, and Lodish teach an isolated hSP polypeptide which is in N-glycosylated form. Tomasetto in view of Podolsky, Alberts, Hitzeman, and Lodish do not teach a pharmaceutical composition comprising an isolated hSP polypeptide which is in N-glycosylated form and a pharmaceutically acceptable carrier.

Jorgensen teaches a pharmaceutical composition comprising PSP and a pharmaceutically acceptable carrier (page 232, full paragraphs 1 and 2; page 233, full paragraph 2; paragraph bridging pages 233-234; page 234, full paragraph 1). PSP inhibits gastrointestinal motility and gastric acid secretion (page 231, full paragraph 1). PSP is atoxic and effective after oral administration. PSP may possess a potential utility in the treatment of gastro-duodenal ulcer diseases. Page 243, full paragraph 1. Jorgensen does not teach in the sense that Jorgensen does not anticipate a pharmaceutical composition comprising an isolated hSP polypeptide which is in N-glycosylated form and a pharmaceutically acceptable carrier.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an isolated hSP polypeptide which is in N-glycosylated form, as taught by Tomasetto in view of Podolsky, Alberts, Hitzeman, and Lodish, and to modify that teaching by making a pharmaceutical composition comprising an isolated hSP polypeptide which is in N-glycosylated form and a pharmaceutically acceptable carrier, as taught by Jorgensen, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make

this modification because PSP, mSP and hSP are expected to fulfill similar biological functions. The invention is prima facie obvious over the prior art.

Claims 27, 29-31, 33, 40, 60-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomasetto (2, cited by Applicants) in view of Podolsky (A), Alberts (u6), Hitzeman (x6), and Lodish (w6) as applied to claims 27, 29, 30, 40, 60-62, and further in view of Onda (n6), Strausberg (C), and Gelfand (B).

Tomasetto in view of Podolsky, Alberts, Hitzeman, and Lodish teach an isolated hSP polypeptide which is in N-glycosylated form, glycosylated at an Asn present at position 15, comprising a glycosylated side chain comprising at least one hexose unit, wherein the glycosylated side chain comprises at least one mannose unit, wherein the glycosylated form comprises two units of GlcNAc. Tomasetto in view of Podolsky, Alberts, Hitzeman, and Lodish do not teach an isolated hSP polypeptide which is in N-glycosylated form, glycosylated at an Asn present at position 15, comprising a glycosylated side chain comprising at least one hexose unit, wherein the glycosylated side chain comprises at least one mannose unit, wherein the glycosylated form comprises two units of GlcNAc, wherein the glycosylated side chain comprises 13-17 mannose units, wherein the glycosylated form comprises $(GlcNAc)_2(Man)_{10-15}$.

Onda discloses the expression and secretion of a recombinant human polypeptide in E. coli, yeast cells, and animal cells (page 3, full paragraph 1; page 4, line 55; sentence bridging pages 4-5; page 5, lines 8-9 and 31-34; Example 5, pages 9-10). Onda's polypeptide has high homology with pancreatic spasmolytic polypeptide (PSP) and can be expected to fulfill similar biological functions (page 6, full paragraph 3).

The use of yeasts such as Saccharomyces as hosts for expressing mammalian and other foreign proteins offers advantages lacking in more commonly used prokaryotic hosts such as Escherichia coli. See Strausberg, column 1, full paragraph 2.

Mammalian cells are more difficult to culture than yeast. See Gelfand, column 2, lines 29-30.

Onda, Strausberg, and Gelfand do not teach an isolated hSP polypeptide which is in N-glycosylated form, glycosylated at an Asn present at position 15, comprising a glycosylated side chain comprising at least one hexose unit, wherein the glycosylated side chain comprises at least one mannose unit, wherein the glycosylated form comprises two units of GlcNAc, wherein the glycosylated side chain comprises 13-17 mannose units, wherein the glycosylated form comprises $(GlcNAc)_2(Man)_{10-15}$.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an isolated hSP polypeptide which is in N-glycosylated form, glycosylated at an Asn present at position 15, comprising a glycosylated side chain comprising at least one hexose unit, wherein the glycosylated side chain comprises at least one mannose unit, wherein the glycosylated form comprises two units of GlcNAc, as taught by Tomasetto in view of Podolsky, Alberts, Hitzeman, and Lodish, and to modify that teaching by expressing an hSP polypeptide in yeast with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because yeasts are useful for the recombinant expression of PSP homologous peptides, yeasts offers advantages lacking in more commonly used prokaryotic hosts such as Escherichia coli, and mammalian cells are more difficult to culture than yeast. In so doing one of ordinary skill in the art would obtain an isolated hSP

polypeptide which is in N-glycosylated form, glycosylated at an Asn present at position 15, comprising a glycosylated side chain comprising at least one hexose unit, wherein the glycosylated side chain comprises at least one mannose unit, wherein the glycosylated form comprises two units of GlcNAc, wherein the glycosylated side chain comprises 13-17 mannose units, wherein the glycosylated form comprises $(GlcNAc)_2(Man)_{10-15}$ because N-linked oligosaccharides can have as many as 60 mannose residues in yeast. The invention is prima facie obvious over the prior art.

Claims 27, 42, 56, 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomasetto (2, cited by Applicants) in view of Podolsky (A), Alberts (u6), Hitzeman (x6), and Lodish (w6) as applied to claims 27, 42, and further in view of Potter (C).

Tomasetto in view of Podolsky, Alberts, Hitzeman, and Lodish teach an isolated hSP polypeptide which is in N-glycosylated form, glycosylated at an Asn present at position 15, comprising a glycosylated side chain comprising at least one hexose unit, wherein the glycosylated side chain comprises at least one mannose unit, wherein the glycosylated form comprises two units of GlcNAc. Tomasetto in view of Podolsky, Alberts, Hitzeman, and Lodish do not teach an isolated hSP polypeptide which is in N-glycosylated form, glycosylated at an Asn present at position 15, comprising a glycosylated side chain comprising at least one hexose unit, wherein the glycosylated side chain comprises at least one mannose unit, wherein the glycosylated form comprises two units of GlcNAc, wherein the hSP is identical to the amino acid sequence of SEQ ID NO: 1 except for the deletion of one or more amino acids at either end of SEQ ID NO: 1. However, it would have been obvious to one of ordinary skill in the art at the

time of Applicants' invention to delete one or more amino acids at either end of SEQ ID NO: 1 with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because it is routine to shorten peptides at the C-terminus or at the N-terminus or at both termini in order to obtain shorter peptides having the same biological effect. See, for example, Potter column 40, penultimate paragraph. It should be understood that various changes and modifications as would be obvious to one having the ordinary skill in this art may be made without departing from the scope of the invention which is set forth in the claims appended hereto. For example, biologically active fragments of such proteins, shortened at the C-terminus or at the N-terminus or at both termini, can be employed instead of the entire protein to have the same biological effect of modulating the bioactivity CRF. The invention is prima facie obvious over the prior art.

Claim Rejections - 35 USC § 112

Claims 43-51, 53-55 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Support for the specific limitations in claims 44, 47, 49, 53-55 and for the combinations of limitations represented by claims 42-45, claims 42, 43, 49-51, claims 42, 43, 49, 52, and claims 42, 46-48 cannot be found in the disclosure as originally filed and the introduction of such limitations raises the issue of new matter. Applicants argue that support for added claims 42-65 is found at page 5, line 29 to page 6, line 18 (claims 42-55), at page 3, lines 24-26 (claims

56-59, and in claims 28-33 (claims 60-65). Applicant's arguments have been fully considered but they are not persuasive. The specification only supports the substitution or creation of glycosylation sites, and not any and/or all substitutions or the combinations of such limitations.

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the limitation "the nucleic acid sequence that encodes SEQ ID NO: 1." The definite article "the" denotes a single, specific nucleic acid sequence. However, due to the degeneracy of the genetic code there are an astronomical number of nucleic acid sequences encoding SEQ ID NO: 1. It is unclear which single, specific nucleic acid sequence is intended. The metes and bounds are not clearly set forth. Claims 28-33, 36, 40-65 depend from claim 27 and also share its deficiency. Claims 27-33, 36, 40-65 are rejected under 35 USC § 112, second paragraph.

Claims 43-45, 51, 52, 54 recite the limitation "first trefoil domain". There is insufficient antecedent basis for this limitation in the claims.

Claims 46-50, 55 recite the limitation "second trefoil domain". There is insufficient antecedent basis for this limitation in the claims.

Claim Objections

Claims 45, 48, 50, 51 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. A non-substituted amino acid sequence fails to further limit a substituted amino acid sequence.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (571) 272-0887.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
AFTER FINAL (703) 872-9307

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
APRIL 8, 2004